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THE RELATION BETWEEN SWEATING AND THE CATECHOL CONTENT OF THE BLOOD IN THE HORSE

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In previous publications it has been shown that there are grounds for the belief that the sweat glands of the horse normally respond to the presence of adrenaline in the blood rather than to the action of secretory nerves (Lovatt Evans & Smith, 1954, 1956), and a preliminary communication by the present authors (1955) suggested that at least part of the sweating response to exercise must be attributable to that cause. The present investigation is an extension of these preliminary trials.

METHODS

Eleven adult horses were used. 15 ml. of blood were drawn aseptically from the jugular vein (at a previously procainized site) and, for the catechol estimations, at once mixed with 5 ml. of a sterile solution containing either 2 g sodium fluoride and 3 g sodium thiosulphate per 100 ml., or 1 g sodium ethylene diaminetetracetate (at pH 7) and 2 g sodium thiosulphate: the latter solution was preferred. The drawing of blood caused no distress or restlessness. The blood mixture was centrifuged for 10 min at 1500 rev/min, and the plasma drawn off with aseptic precautions; the plasma was kept under refrigeration until the analyses for adrenaline and noradrenaline were made by the method of Weil-Malherbe & Bone (1953). The analytical error of this method is of the order of $\pm 10\%$. Inexplicably high figures were occasionally obtained, and these have been noted, but no conclusions drawn from them. No such high results were obtained during many hundreds of analyses of normal human plasma.

Evidence in favour of the validity of the method for estimations in plasma has been summarized (Weil-Malherbe, 1955). It is particularly significant that practically identical results are obtained in plasma with this method and with that of Lund (1949, 1950). With acid-hydrolysed urine different results are obtained, the former giving the higher values (von Euler, von Euler & Floding, 1955), which suggests that the interfering substances present in acid-hydrolysed urine are not present in appreciable quantities in plasma. Approximate estimates of the red cell volume were made from measurements in the centrifuge tube, allowance being made for the diluent fluid. In a few instances actual readings (using haematocrit tubes) of packed red cell volume were made, and these showed that the rough estimates of changes were substantially correct.

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RESULTS

Blood catechols in resting horse plasma. Table 1 gives the results of thirty-two estimations. Horse no. 8 gave exceptionally high values, on two occasions, for both the catechols. These figures we cannot explain. Four other horses on the same cold, dry day gave normal figures, and horse no. 8 on another, slightly warmer, day also gave more usual values.

TABLE 1. Adrenaline and noradrenaline content of horse plasma

Horse no.	μg/l. plasma				Temp. (° C)		
		Adrenaline		Noradrenaline	Dry-bulb	Wet-bulb	r.h.
1	Mean 1·67	1·22	Mean 4·85	3·58	7·1	6·4	90
		1·62		6·41	2·7	2·5	98
		2·36		5·46	1·1	0·0	79
		1·67		5·10	6·6	4·8	74
		1·50		4·05	10·6	7·3	59
		1·72		5·85	17·2	14·1	69
		1·63		3·50	12·8	11·7	86
2	Mean 1·63	1·10	Mean 4·85	3·72	7·1	6·4	90
		1·33		4·58	2·7	2·5	98
		1·54		4·48	9·6	9·5	98
		1·53		5·96	1·1	0·0	79
		1·58		5·70	6·6	4·8	74
		2·68		4·68	12·8	11·7	86
3	Mean 1·68	1·67	Mean 4·50	4·28	2·7	2·5	98
		1·68		4·72	9·6	9·5	98
4		1·56		5·25	2·7	2·5	98
5		1·27		3·76	9·6	9·5	98
6		1·25		5·35	9·6	9·5	98
7	Mean 1·73	1·34	Mean 5·63	5·25	9·6	9·5	98
		1·86		6·55	1·1	0·0	79
		1·52		4·66	6·6	4·8	74
		1·84		7·32	10·6	7·3	59
		2·07		6·95	17·2	14·1	69
		1·77		3·05	12·8	11·7	86
8		1·39		5·10	9·6	9·5	98
		*14·40		*28·80	1·1	0·0	79
		*4·04		*25·2	6·6	4·8	74
9	Mean 2·00	1·57	Mean 6·27	5·47	9·4	9·5	98
		1·50		5·52	1·1	0·0	79
		2·94		7·82	6·6	4·8	74
10		1·65		4·82	12·8	11·7	86
11		2·42		4·80	12·8	11·7	86
	Mean excluding*	1·693	Mean excluding*	5·125			

Excluding these exceptional values the mean values were: for plasma adrenaline 1·69μg/l., S.D. 0·424μg/l. and for noradrenaline 5·13μg/l., S.D. 1·14μg/l. The correlation coefficient between pairs of values is 0·451, which, with 28 degrees of freedom, lies nearly on the 1% level of significance, i.e. the adrenaline and noradrenaline are associated.

The proportions of adrenaline and noradrenaline are thus in the ratio of about 1 to 3. In the horse adrenal, according to West (1953), the proportion of adrenaline in the medulla to the noradrenaline is about 4:1 (3200 and 800μg/g respectively). Various inferences might be drawn from this, but as it is by no means certain that at least some of the plasma noradrenaline might not be of peripheral origin, no firm conclusion can be drawn.

There was no regular difference in adrenaline or noradrenaline content from one animal to another, or from day to day in the same animal, and the drawing of blood caused no significant cardiac acceleration or other evidence that might suggest increased adrenal activity.

The effect of exercise. In these experiments, the first sample of blood was drawn, at a previously procainized site, from the jugular vein. The animal, ready saddled, was then ridden at a steady canter for the required time, and at least until free sweating was established, and then, as soon as possible (usually about 3 min) afterwards, the second sample was drawn. (Table 2, Expts. 1–11). In two experiments (Table 2, Expts. 12 and 13) a third sample was taken about 20 min after the end of exercise.

The results show that in every case there was an increase in both adrenaline and noradrenaline in the plasma. In one instance (Expt. 7) the rises were very large. This animal was less fit than the others, and on this occasion showed some respiratory distress during the ride, and refused to canter for any length of time: the high figures might therefore be acceptable as genuine, and perhaps attributable to a transitory anoxia. If these two high post-exercise values for both the catechols are excluded, the averages show a rise in adrenaline from 1·41 to 2·50μg/l. (or 78%), and in noradrenaline from 4·48 to 6·96μg/l. (or 56%).

Statistical examination shows that the increases in plasma adrenaline and noradrenaline after exercise are highly significant, and more so if the results of Expt. 7 are excluded. It also shows that there is a close correlation between the increases in adrenaline and noradrenaline. The following data illustrate these points:

Plasma adrenaline

(*a*) Including Expt 7. Mean difference 2·056μg/l.; S.E. of mean difference 0·808μg/l.; $t_{(12)} = 2{\cdot}54$; $P = 0{\cdot}03$.

(*b*) Excluding Expt 7. Mean difference 1·279μg/l.; S.E. of mean difference 0·242μg/l.; $t_{(11)} = 5{\cdot}28$; $P < 0{\cdot}001$.

Plasma noradrenaline

(*a*) Including Expt 7. Mean difference 4·479μg/l.; S.E. of mean difference 2·128μg/l.; $t_{(12)} = 2{\cdot}105$; P *c.* 0·05.

(*b*) Excluding Expt 7. Mean difference 2·4125μg/l.; S.E. of mean difference 0·551μg/l.; $t_{(11)} = 4{\cdot}38$; $P < 0{\cdot}001$.

TABLE 2. Adrenaline and noradrenaline contents of plasma before and after exercise (without and with atropine)

Expt. no.	Horse no.	Exercise (min)	Haematocrit, % reds: Before	After	Plasma adrenaline (μg/l.): Before	After	Plasma noradrenaline (μg/l.): Before	After	Air temp. (° C): Dry-bulb	Wet-bulb	r.h.	Remarks
1	1	20	39	44	1·22	1·26	3·58	3·81	7·1	6·4	90	Fit horse, regularly ridden. Sweated freely after trotting and cantering.
2	1	27	35	50	1·62	1·87	6·41	6·50	2·7	2·5	98	Sweated well; no lathering
3	2	20	36	48	1·10	1·52	3·72	4·18	7·1	6·4	90	Fit horse, regularly ridden and always a free sweater. Keen temperament
4	2	32	30	50	1·33	3·84	4·58	8·70	2·7	2·5	98	—
5	2	65	28	48	1·54	3·12	4·48	6·82	9·6	9·5	98	—
6	3	19	33	45	1·67	2·03	4·28	5·00	2·7	2·5	98	Not thoroughly fit. Exceptionally free sweater on light exercise
7	3	50	34	52	1·68	12·90	4·72	34·00	9·6	9·5	98	Sweated very freely; some distress and refused to canter
8	4	36	31	44	1·56	3·12	5·25	10·60	2·7	2·5	98	Sweated freely, but less than 2 or 3
9	5	52	31	45	1·27	2·60	3·76	8·65	9·6	9·5	98	Not completely fit and blew considerably. Sweated freely.
10	6	52	30	39	1·25	3·04	5·35	9·00	9·6	9·5	98	Sweated moderately
11	7	20	32	44	1·34	2·59	5·25	6·34	9·6	9·5	98	Bucked most of the time, but sweated freely
		Mean	32·5	46·2	1·41	3·45	4·48	9·40				
12	7	15	40	56	(1) 1·77	(2) 3·60	(1) 3·05	(2) 6·95	12·8	11·7	86	Sample 2 taken 5 min after exercise
12	7	15	40	52		(3) 2·73		(3) 2·75	12·8	11·7	86	Sample 3 taken 20 min after exercise
13	1	15	44	61	(1) 1·63	(2) 4·06	(1) 3·50	(2) 5·61	12·8	11·7	86	Sample 2 taken 3 min after exercise
13	1	15	44	47		(3) 2·15		(3) 4·51	12·8	11·7	86	Sample 3 taken 18 min after exercise
14	7	0	36	33	(1) 2·07	(2) 1·35	(1) 6·95	(2) 6·78	17·2	14·1	69	Atropine 0·06 mg/kg 30 min before sample 2
14	7	25	33	48		(3) 2·52		(3) 9·90	17·2	14·1	69	Sample 3 taken 2 min after exercise and 63 min after atropine
15	1	0	38	35	(1) 1·72	(2) 1·36	(1) 5·85	(2) 5·76	17·2	14·1	69	Atropine 0·06 mg/kg 30 min before sample 2
15	1	25	35	49		(3) 2·61		(3) 9·05	17·2	14·1	69	Sample 3 taken 4 min after exercise and 61 min after atropine

Correlation between adrenaline and noradrenaline differences

(*a*) Including Expt. 7. Correlation coefficient $\gamma = 0{\cdot}98$; 11 degrees of freedom; $P < 0{\cdot}01$.

(*b*) Excluding Expt. 7. $\gamma = 0{\cdot}709$; $P = 0{\cdot}01$.

The rise in blood adrenaline persisted for some time after exercise: Expts. 12 and 13 show that 18 or 20 min after the conclusion of the ride, the figures, though considerably lower than at 3 min after, were still significantly higher than when at rest.

The increases in noradrenaline content were less regular than those of adrenaline, but there was always some increase. What the increase in noradrenaline might mean in terms of sweating response it is not possible to state definitely. The substance itself does not cause sweating when administered, but causes hair-erection (Lovatt Evans & Smith, 1956). If given together with adrenaline it does not much modify the resultant sweating, such effect as there is being rather to diminish it.

An invariable accompaniment of exercise was the increase in red cell volume (average 32·5 % rising to 46·2 %), an effect already well known (Scheunert & Krzywanek, 1926).

Exercise after atropine. It is well known that atropine does not affect the sweating due to exercise or to adrenaline administration in horses. In two experiments (Table 2, Expts. 14 and 15), atropine, 0·06 mg/kg, was given between the drawing of samples 1 and 2. This caused a reduction in the amounts of both catechols in the plasma, which may have been due to an effect on cholinergic transmission in the adrenals, though Feldberg, Minz & Tsudzimura (1934) found that, in the cat, the muscarinic component was relatively small. After subsequent exercise, however, the plasma content of both catechols was found to be increased, and to a level higher than that before atropine.

Blood adrenaline and sweating

In all animals so far as we know exercise is accompanied by a discharge of adrenaline (and noradrenaline) into the blood. The results here described refer to the content in venous blood, but it must be supposed that the increases would be still greater in arterial blood. The question remains whether, in fact, the increases in blood adrenaline in the horse are adequate to cause sweating. In order to test this point, adrenaline or noradrenaline was administered intravenously in doses which in the case of adrenaline caused general sweating, and in similar doses with noradrenaline, and the immediate change determined. The samples were drawn from the side opposite to that of injection. The results are given in Table 3.

If we suppose that the hormones are at first confined to the blood stream, and assuming a plasma volume of 25 l., it would be expected that 1 mg. of a

TABLE 3. Plasma catechols before and after intravenous injection of adrenaline or noradrenaline

Expt. no.	Horse no.	Catechol and dose (mg)	Mean time of subsequent samples after dose		Plasma adrenaline (μg/l.)		Plasma noradrenaline (μg/l.)		Haematocrit % R.V.C.		Sweating
			min.	sec	Before	After	Before	After	Before	After	
		Norad.									
16	7	0·5	2	—	1·86	1·88	6·55	6·70	46	50	
17	9	2·0	1	30	1·50	3·32	5·52	8·60	41	41	
18	7	1·0	1	—	1·52	2·41	4·66	12·20	40	41	
19	9	3·0	—	75	2·94	3·50	7·82	22·2	35	39	None
20	10	2·0	3	—	1·65	1·72	4·82	5·52	—	24	
20	10	2·0	8	—	—	1·41	—	6·97	—	19	
20	10	2·0	74	—	—	2·32	—	5·83	—	21	
		Adr.									
21	1	1·0	—	50	1·67	3·94	5·10	8·30	43	43	
22	2	1·0	1	—	1·58	7·50	5·70	14·0	39	43	General
23	8	3·0	—	30	4·04	35·3	25·2	9·2	37	37	
23	8	3·0	1	—	—	32·0	—	6·28	—	37	
24	1	1·0	2	—	2·36	2·09	5·46	6·92	44	58	Profuse
25	2	0·5	2	—	1·53	2·75	5·96	7·50	37	57	Profuse

substance would raise the plasma content by 40μg/l. If distributed equally between blood and 'free water' (say 125 l.), 1 mg would raise the plasma content by 8μg/l.; or if equally between blood and all available water (say 250 l.) by about 4μg/l. The results of Table 3 show some unexpected features. First, the administration of either catechol causes an increase of plasma concentration, not only of that one, but also, though generally of smaller extent, of the other. In Expt. 23 the initial level of noradrenaline was so high as to be in all probability attributable to some error, and this may explain the apparent fall after adrenaline injection. If we select those results in which the second sample was collected in 1 min or less after the adrenaline injection, and ignore the content of the catechol not injected, we get the following figures; expressed as rise in μg/l./mg injected:

Rise in injected catechol

Catechol injected	Time	Rise (μg/l./mg)
Expt. 18. Noradrenaline	1 min	7·54
Expt. 21. Adrenaline	50 sec	2·27
Expt. 22. Adrenaline	1 min	5·92
Expt. 23. Adrenaline	30 sec	10·42
Expt. 23. Adrenaline	1 min	9·32

The figures are merely suggestive, but they show that the catechol substances are swiftly dispersed, probably throughout the whole available tissue water, and are quickly used up. Sweating lasts for some 15–20 min after such injections of adrenaline; long before the end of this period no increase in blood concentration is detectable, and it would seem that extremely small increases in blood adrenaline are able to cause sweating. It seems certain, therefore, that the rise invariably seen after exercise must play an important part in causing sweating.

Blood sugar in exercise. In three experiments the blood glucose was determined by Somogyi's (1945) method before and after exercise, in the expectation that it might be found to increase as a result of the adrenaline liberation. The horses were ridden for 25 min, including 20 min sustained trotting and cantering, and all sweated freely. Sample 2 was taken immediately after exercise, and sample 3 after an hour's rest. The results are given below:

Horse no.	Blood glucose (mg/100 ml.) Rest	After exercise	1 hr later
1	71	71	69
7	78	71	60
10	68	54	68

The results show that there was a fall in blood sugar, or no change, from which it may be inferred that the effect, if any, of adrenaline was at least offset by increased sugar utilization. Similar results have been found in the dog (Brouha, Cannon & Dill, 1939), and in man (Douglas & Koch, 1951).

That adrenaline in amounts adequate to cause sweating causes a rise of blood sugar in the resting animal was ascertained in three experiments kindly carried out at our request by Dr Frank Alexander of the Royal (Dick) School of Veterinary Studies, Edinburgh. The results of one such experiment were as follows:

	Blood sugar (mg/100 ml.)				
Time (min) ...	0	15	30	60	120
Control, without adrenaline	91·5	88·5	88·7	85·7	81·3
After intravenous adrenaline, 1 μg/kg	76·8	91·0	89·3	82·5	78·3

The control shows that the blood sampling produced no rise in blood sugar.

The effect of morphine. It is well known that, in the cat, morphine causes the release of adrenaline (Elliott, 1912), but in the dog this effect does not seem to be demonstrable (Gross, Holland, Carter & Christensen, 1948; Miller, George, Elliott, Sung & Way, 1955). In the horse we never saw sweating result from injections of morphine up to doses of 1 mg/kg, but Dr Frank Alexander informs us that it sometimes occurs, and that he has seen a rise in blood sugar 10 min after a dose of 0·5 mg/kg. The toxic dose of morphine for the horse is said to be about 5 mg/kg, but in these experiments, shown in Table 4, we did not exceed 1 mg/kg.

The results show that the smaller doses of 0·25 and 0·5 mg/kg produced a fall in the blood catechols; the largest dose, of 1 mg/kg, produced a definite rise in both, with considerable cardiac acceleration. In spite of a rise in blood adrenaline which should have been adequate to cause sweating, this did not occur. A possible explanation for this would be that the morphine reduced the sensitivity of the sweat glands to adrenaline, but although this point was tested, the evidence for it was equivocal (Lovatt Evans & Smith, 1956).

The effect of carbachol. Given intradermally, parasympathomimetic drugs cause sweating in the horse, but when given intravenously in small doses, about adequate to cause salivation, do not (Lovatt Evans & Smith, 1954). However, larger doses, or doses preceded by an anticholinesterase, do cause abundant sweating, which can be prevented or stopped by atropine (Lovatt Evans & Smith, 1956). The explanation of the sweating on intradermal injection might well be accounted for by an increase in skin circulation, so that more of the plasma adrenaline got to the skin in unit time, but when given intravenously, it seemed possible that an additional factor might be the release of adrenaline into the blood. Table 5 gives the results of experiments.

The results show in one instance there was no rise, but a fall, in the blood catechols (Expt. 29). In Expts 30 and 31 there was a rise in adrenaline, which was replaced by a fall half an hour after atropine had been given in order to relieve the symptoms. All the horses sweated freely. The content of

TABLE 4. Blood catechols before and after morphine

Expt. no.	Horse no.	Morphine (mg/kg)	Plasma adrenaline (μg/l.)		Plasma noradrenaline (μg/l.)		Effect on sweating	Remarks
			Before	After	Before	After		
26	8	0·25	1·39	0·69	5·10	4·42	No sweating	Sample 2 taken 10 min after morphine
27	9	0·50	1·57	0·07	5·47	3·26	No sweating	Sample 2 taken 10 min after morphine
28	11	1·00	2·42	5·62	4·80	12·50	No sweating	Sample 2 taken 4 min after morphine. Heart rate accelerated 57–96. No excitation

TABLE 5. Effect of carbachol on plasma catechols

Expt. no.	Horse no.	Carbachol dose (mg/kg)	Time of sample after carbachol (min)	Plasma adrenaline (μg/l.)			Plasma noradrenaline (μg/l.)			Atropine, mg/kg, and time after carbachol, min
				(1) Before	(2) After	(3) After atropine	(1) Before	(2) After	(3) After atropine	
29	2	0·004	5	2·68	2·12	1·89	4·68	4·47	5·76	0·06; 23 min; sample (3) 11 min after atropine
30	7	0·004	3½	1·84	2·31	—	7·32	8·85	—	0·04; 6 min; sample (3) 32 min after atropine
30	7	0·004	5½	—	2·98	1·33	—	8·18	4·90	
31	1	0·004	1	1·50	2·48	—	4·05	3·96	—	0·06; 7 min; sample (3) 28 min after atropine
31	1	0·004	6	—	1·98	1·24	—	5·85	5·79	

noradrenaline was less affected after carbachol, and showed a slight fall in two cases; it was also less affected by atropine. The rises in blood adrenaline in two cases out of three would have been adequate to cause sweating.

DISCUSSION

The experiments indicate a close relationship between the adrenaline content of the blood and the incidence of sweating. The only exception was in the action of morphine, which does not regularly cause sweating, but which does, when given in sufficient dose, raise the blood adrenaline. The invariable rise in the adrenaline content of the blood which results from exercise, or from the administration of sufficiently large doses of carbachol, adds further support to the arguments brought forward by Lovatt Evans & Smith (1956) that the sweat glands of the horse are normally caused to function humorally, and not as a result of the receipt of nervous impulses to the sweat glands.

The content of noradrenaline generally varies with that of adrenaline, but there are no indications that it plays any part in the causation of sweating, since noradrenaline does not cause sweating when administered; its functions are more probably related to the regulation of the circulation, as is generally supposed.

It is hoped that a further study may throw some light on the problem of the tropical anhidrosis in horses; this might be due either to a reduced sensitiveness of the sweat glands to adrenaline, or to a reduced liberation of adrenaline in exercise, or to both factors.

SUMMARY

1. The plasma of the horse at rest contains, on the average, about 1·7 μg/l. adrenaline and 5·1 μg/l. noradrenaline.

2. In exercise causing free sweating there is a rise in blood adrenaline of about 78 % and in noradrenaline of about 56 %.

3. Atropine, 0·06 mg/kg, lowers the concentration of both catechols at rest, but does not prevent the rise on exercise, and does not check exercise sweating.

4. Intravenous injection of adrenaline or of noradrenaline (1–7 μg/kg) causes such increases in catechol content of the blood as to suggest rapid dispersal and utilization of the injected catechol. The level of both catechols was raised by the injection of either.

5. The blood sugar was not raised on exercise, though it was increased at rest by amounts of adrenaline which caused sweating (1 μg/kg).

6. Morphine did not cause sweating when given in the small doses of 0·25–1·0 mg/kg; with the largest dose there was a rise, but with the smaller doses a fall in blood adrenaline.

7. Carbachol, 0·004 mg/kg caused free sweating (prevented by atropine), and in two cases out of three a rise in blood adrenaline.

8. The noradrenaline concentrations in the blood generally vary with the adrenaline content, but are probably not directly correlated with sweating. The adrenaline concentrations are probably directly correlated with sweating, and support the view that the sweat glands of the horse are humorally controlled.

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